Large-Scale Grid Computing for Biomedical Drug Discovery: A Case Study on Virtual Screening With Smallpox Topoisomerase-I

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Despite its elimination in 1977 through vaccination, the Smallpox virus still poses a threat as a weapon of bioterrorism. Even though government agencies have been stockpiling vaccines, mass vaccination has many drawbacks such as delay in efficacy and the risk of damaging side effects. Therefore, developing small molecule drugs to counter the attack of Smallpox is imperative as an alternative therapy. Although smallpox-encoded enzyme, topoisomerase-I, has been shown to amend itself to rational drug development, to date there has been very little characterization of molecular libraries against this target. Molecular libraries such as the library of 35 million molecules developed at the University of Oxford provide a rich means of exploring the chemical space towards finding small molecules as possible leads. This 35-million library of "drug-like" small molecules is sourced from various chemical catalogs and combinatorial libraries. Experimental testing of such libraries using traditional drug discovery methodologies would be a very lengthy, laborious and prohibitively expensive process. Predictive *in silico* technologies, such as virtual screening on the other hand, help reduce the domain of this chemical space amenable for experimental testing. However, virtual screening of this large chemical space requires a vast amount of computational time – an equally expensive and time-consuming approach. The United Devices' grid-computing platform uses a very novel approach to solve such problems as virtual screening, very inexpensively and in a short amount of time. United Devices' Grid MP software makes enormous amounts of compute power available at a very low cost. At present, virtual screening of a library of 35 million compounds against topoisomerase-I is being conducted. In just six months, over 30,000 years of compute time have been accumulated for this project via United Devices' public grid, Grid.org - a throughput that is not possible with conventional compute technologies. A grid-enabled version of the LigandFit application from Accelrys is being used to orient these small molecules into the active sites of topoisomerase-I and evaluate docking scores between the protein active sites and ligand atoms. Using LigScore, several scoring functions that capture the physicochemical interactions between active site atoms and small molecules are also being calculated. A consensus score of these functions is being constructed. Our preliminary analysis of the results on the virtual screen suggests that there is more than a **100-fold reduction** of the library from 35 million to a manageable number of hits ranked on a consensus score probability basis, that can then be optimized to generate leads. As every molecule in the library is synthesizable, it is possible to test this limited set of hits in experiments. This smaller set of compounds will be presented to the Department of Defense in September 2003. This novel grid computing approach promises to have a tremendous impact on virtual screening. Several examples such the project listed above have already shown that these types of virtual screens can now be done routinely. It is hoped that many large compound libraries can now be characterized across many protein targets, yielding substantially more knowledge about these compounds and their interaction with targets.

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